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TITLE: Detection of Brain Reorganization in Pediatric Multiple Sclerosis Using Functional MRI

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CONTRACTING ORGANIZATION:
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Due to slower than expected study recruitment and imaging of patient cohort, progress over the 2015 funding period was delayed. This resulted in a 12-month extension over which time the main study conclusions are planned to be completed. Despite the incomplete cohort, we performed preliminary study using a smaller cohort and made significant findings which support the main objectives of the planned research. Significant findings include: 1) detection of brain organization in a cohort of 24 pediatric onset multiple sclerosis patients (POMS) and 25 healthy controls demonstrated congruency between fMRI mappings and patient performance; 2) testing of the fMRI methods we developed for use in POMS patients was carried out in a group of 42 presurgical pediatric patients at our institution, demonstrating reliable fMRI mappings of language and motor systems using our methods in the pediatric brain.

Item 1: we found that 12 of 12 POMS patients presenting with mild to severe deficits as measured by neuropsychological exam also demonstrated abnormal brain function as measured by our fMRI methods. These preliminary findings support our project hypothesis that POMS patients who suffer from impairment will also demonstrate abnormal fMRI mappings.

Item 2: the information provided to surgeons by our fMRI methods allowed the potential to spare pediatric patients post-operative impairment in any language or motor functions that were located near a planned surgical site.

15. SUBJECT TERMS

Functional brain mapping using fMRI, functional magnetic resonance imaging (fMRI), pediatric-onset multiple sclerosis (POMS),

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1. **INTRODUCTION:**

The goal of this research is to assess the capability of the pediatric brain to respond to brain injury suffered during MS disease progression. In this study we focus on the characterization of adaptive functional reorganization as a way to explain how some early-stage MS patients are able to perform well in clinical cognitive testing despite the accumulation of underlying brain injury; and furthermore, why later-stage patients often suffer a sharp decline in cognitive performance. We aim to examine the phenomena of adaptive reorganization of vital abilities, as a potential biological mechanism supporting the favorable clinical courses seen in some MS patients compared to others. By quantifying the strategies used to redistribute primary motor, visual, and language function, we aim to develop new techniques for monitoring the impact of disease progression on these functional systems in individual patients. As tools to accomplish this, we apply comparative assessments of fMRI mappings of language, memory, and motor function, and performance on clinical neurocognitive examinations. Our research represents an innovative application of fMRI functional mapping in the evaluation of MS in young patients. The prospective study aims to assess fMRI activation patterns in 30 POMS patients and 40 healthy control volunteers as a method for understanding the correlations between abnormal functional activation by fMRI and performance indicators measured by standard neuropsychological tests.

The project goals have been delayed due to backlog in MRI scanning of patients and volunteers at our institution—we are behind schedule in recruiting and collecting data in 10 of 40 volunteers, and an additional 5 of 30 POMS patients. We are presently in a 12 month no-cost extension over which time we plan to complete the remaining tasks as outlined in our original statement of work (SOW). In particular, we are presently behind schedule on the collecting of healthy volunteer's data. Because our project relies upon the control data from healthy volunteers to compare against the POMS patient data, the lack of a complete control dataset has delayed Task 1, Task 2, and Task 3 goals. In the meantime however, we have been able to test, and further explore the fMRI methodologies developed under this project in related pediatric patient populations including presurgical epilepsy patients.

2. **KEYWORDS:** Magnetic Resonance Imaging (MRI); functional MRI (fMRI); multiple sclerosis (MS); pediatric onset MS (POMS); auxiliary activation ratio (AAR); lateralization index (LI)

3. **ACCOMPLISHMENTS:**

   a. **What were the major goals of the project?**

      i. Task 1. Acquisition and analysis of control data from healthy volunteers, including the formation of normative consensus fMRI activation maps for subsequent comparison against POMS patient's activation maps (months 1-12):

         a) Subtask 1a. Initiate regulatory review and approval process to include local Institutional Review Board and Department of Defense Human Research Protection Office for the use of human subjects (months 1-3).

b) Subtask 1b. Recruit 40 healthy volunteers from the local community at a target rate of 13 volunteers per quarter period; acquire fMRI data for language, memory, and visual-motor functions (months 3-12).

c) Subtask 1c. Acquire neuropsychological testing of the 40 healthy volunteers (months 3-12).

d) Subtask 1d. Determine normative values for fMRI lateralization based on the average laterality index from the 40 healthy volunteers; determine mean lateralization index (LI) for language, memory, and visual-motor tasks (months 8-12).

e) Subtask 1e. Perform statistical analysis of normative fMRI maps from the 40 healthy volunteers in order to form consensus fMRI activation maps for language, memory, and visual-motor tasks (months 8-12).

f) Subtask 1f. Prepare publication to disseminate our findings from the evaluation of normative fMRI activation patterns in healthy pediatric volunteers for language, memory, and visual-motor processing.

ii. Task 2. Acquisition and comparison of fMRI activation patterns in 30 POMS patients against normative patterns recorded in healthy controls (months 3-21):

a) Subtask 2a. Recruitment of 30 POMS patients at a target rate of 5 patients per quarter period; acquire fMRI data for language, memory, and visual-motor functions (months 3-21).

b) Subtask 2b. Acquire neuropsychological testing of the 30 POMS patients (months 3-21).

c) Subtask 2c. Determine Auxiliary Activation Ratios (AAR) for each of the 30 POMS patients based on the comparison against normative consensus fMRI activation maps for language, memory, and visual-motor functions (months 3-21).

d) Subtask 2d. Compare individual LI values for each of the 30 POMS patients against the normative mean LI values determined from healthy volunteers (see Subtask 1e.), for language, memory, and visual-motor functions (months 3-21).

e) Subtask 2e. Prepare publication to disseminate our findings from the comparison of fMRI activation patterns in POMS patients against healthy controls for language, memory, and visual-motor processing (months 18-21).

iii. Task 3. Correlation of fMRI metrics in 30 POMS patients with neuropsychological performance scores (months 18-24):

a) Subtask 3a. Incorporate AAR and LI metrics from POMS patients into statistical regression model against neuropsychological scores for language, memory, and visual-motor functions; use leave-one-out strategy to assess the predictive strength of proposed fMRI metrics (months 18-24).

b) Subtask 3b. Prepare publication to disseminate our findings in regression model analysis of the proposed fMRI metrics for predicting performance decline in POMS (months 18-21).

iv. Task 4. Apply for and secure additional funding in order to pursue the long-term objectives of the proposed research (months 12-24):

a) Subtask 4a. Use the findings from the proposed cross-sectional study to develop compelling applications to The National Institutes of Health (NIH) by way of K and R01 funding mechanisms in order to carry out longitudinal study of MS patients in translational assessment of the proposed methodologies (months 12-24).

b. **What was accomplished under these goals?**

i. Task 1. We have recruited and scanned 30 healthy volunteers. This number however falls short of our target 40 healthy controls. We have not yet performed consensus maps from the healthy data because we must first collect our POMS cohort and carefully age- and sex-match the healthy cohort to the POMS cohort. We are however able to recruit and scan healthy volunteers without much delay---POMS patients are slightly more challenging to recruit for the study.

a) Subtask 1a. In 2015 we underwent Institutional Review Board (IRB) Continuing Review. This review was approved on 7/26/2015, thereby extending the expiration of this IRB to 7/26/2016. As such, we have successfully obtained and presently retain Institutional Review Board and Department of Defense Human Research Protection Office for the use of human subjects.

b) Subtask 1b. We have recruited and acquired fMRI data for language, memory, and visual-motor functions in 30 healthy volunteers. This group is incomplete as it falls short of the 40 target. We plan to complete this target group over the 12 month extension and completion of Subtask 1b.

c) Subtask 1c. Control volunteers needed to be recruited after the POMS population is completed so that they can be properly age-, and sex-matched. We are therefore behind schedule in compiling normative neuropsychological data on the control group. We plan

to complete the target control group over the 12 month extension and completion of Subtask 1c.

d) Subtask 1d. We have determined normative values for fMRI lateralization of language on 25 healthy volunteers; however, we must now wait until our POMS population is complete in order to recruit the additional healthy controls. As we are delayed with patient recruitment and with healthy control recruitment. We plan to complete the target control group over the 12 month extension and completion of Subtask 1d.

e) Subtask 1e. We have not yet performed the statistical analysis of normative fMRI maps from the 40 healthy volunteers as our target recruitment is behind schedule and presently incomplete. We plan to complete the target control group over the 12 month extension and completion of Subtask 1e.

f) Subtask 1f. As the control group is presently incomplete, we have not yet published our main normative findings in healthy volunteers over the 2015 funding period—however, we have previously published on preliminary data in the first 25 healthy controls in our 2014 publication (Suarez RO et al, 2014). We plan to complete the target control group of 40 over the 12 month extension and completion of Subtask 1f.

ii. Task 2. We successfully recruited and consented 30 POMS patients of the target 30 total for the project; however due to scheduling delays, of these 30, we have only acquired fMRI in 25 thus far.

a) Subtask 2a. We have presently recruited 30 POMS, 5 of whom still need to have fMRI acquired. We are behind schedule with this subtask, but we expect to complete subtask 2a in the first quarter of the 12-month no cost extension.

b) Subtask 2b. Of our 30 POMS cohort recruited, we have neuropsychological testing of 24 POMS patients. We expect to acquire the additional 6 POMS neuropsychological testing by the end of the second quarter during the 12-month no cost extension.

c) Subtask 2c. We have not yet calculated Auxiliary Activation Ratios (AAR) for each of the POMS patients. This requires the consensus control map of 40 healthy volunteers and a completed dataset of 30 POMS patients.

d) Subtask 2d. We compared individual functional lateralization index (LI) values for 24 POMS patients against the normative mean LI values determined from 25 healthy volunteers (see Subtask 1e.), for language and motor function. This analysis demonstrated that POMS patients who suffer from mild to severe language or motor impairments demonstrated abnormal fMRI

activation patterns. This is a significant finding which directly supports the hypothesis behind our project. Figures 1 and 2 below illustrate our preliminary findings in pursuit of subtask 2d.

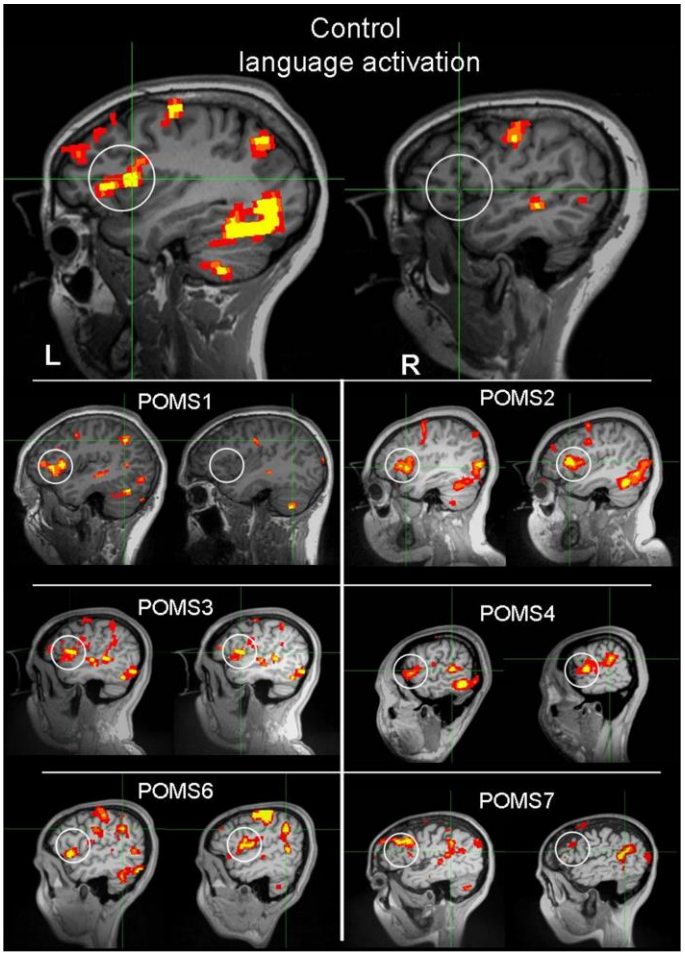

Figure 1: Language-specific fMRI activation patterns from visually presented vocalized antonym-generation (uncorrected, $p < 0.05$) overlaid on T1-weighted anatomical images, for healthy control subjects (labeled: Control) and in 6 POMS patients (labeled: POMS1, POMS2, POMS3, POMS4, POMS6, and POMS7). The normative activation in the inferior frontal gyrus of the control subject is consistent with the left-dominant expressive language center (white circles). In contrast, the abnormal activation observed in POMS2, POMS3, POMS4, and POMS6 patients are significantly different from the normative pattern. Note a normal pattern of activation recorded in POMS1 and POMS7.

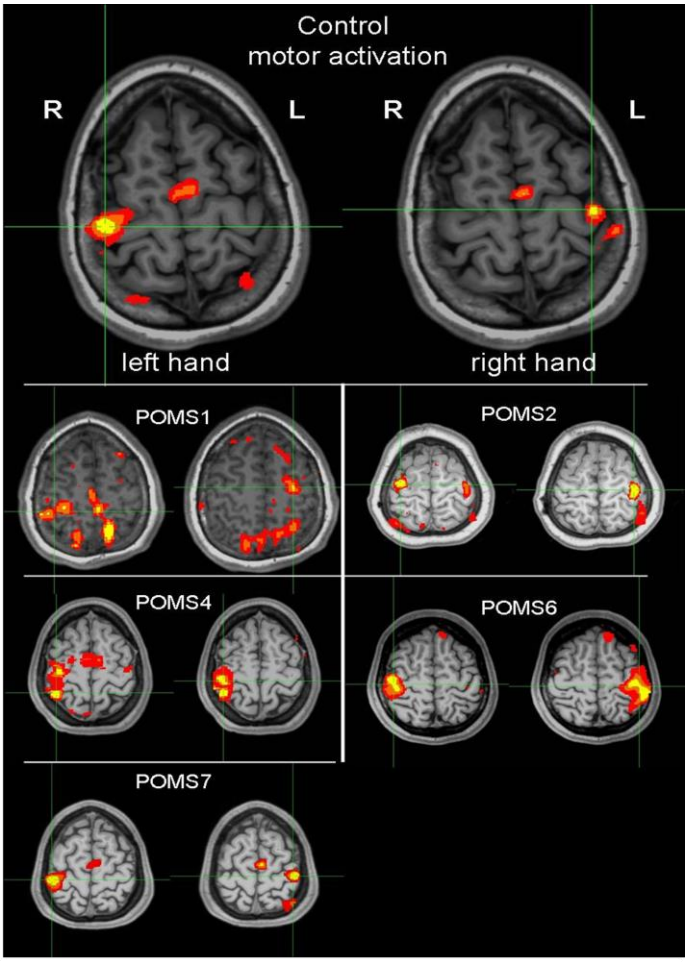

Figure 2: FMRI activation mappings of primary motor cortex (uncorrected, $p < 0.01$) overlaid on T1-weighted anatomical images, for healthy control subjects (labeled: Control) and in 5 POMS patients (labeled: POMS1, POMS2, POMS4, POMS6, and POMS7). Note the abnormal motor fMRI activation patterns in POMS1 and POMS4 patients which are significantly different from the normative pattern recorded in the healthy brain. Note a normal pattern of activation recorded in POMS2, POMS6, and POMS7.

In this preliminary study we performed a comparative study of POMS patients against age- and gender-matched healthy controls and were able to confirm our hypothesis that POMS patients presenting with mild to severe language or primary motor deficits also demonstrate abnormal brain function by fMRI.

e) Subtask 2e. Due to delays in completing our targeted cohorts of controls and POMS patients, we have not yet published the main findings of our project. We expect to complete subtask 2e in the 12-month no cost extension period.

ii. Task 3. We have not yet performed a full correlation of fMRI metrics in POMS patients with neuropsychological performance scores due to incomplete datasets. We have however done preliminary studies on the incomplete group data and were able to confirm trends that support our original hypothesis. These are compelling findings that will likely generalize to the targeted number or participants once our recruitment is goals are reached. We plan to complete the analysis once our targeted numbers are met in the 12-month no cost extension period.

a) Subtask 3a. Figure 3 below illustrates our preliminary findings when comparing fMRI activation patterns to neuropsychological testing scores in a smaller group of POMS patients.

In this preliminary study, fMRI localization and lateralization metrics for language and primary motor tasks were utilized in healthy control volunteers and 12 age- and sex-matched POMS patients. The POMS patients' results were evaluated for abnormal language and/or primary motor activation patterns. FMRI-derived metrics in POMS patients were compared with performance indicators from neuropsychological evaluations. FMRI activation patterns were assessed to detect abnormal cortical recruitment and by this means predict potential pre-clinical deficits in the POMS patients.

To assess the neuropsychological state of the patients, a battery of tests was administered, including the Wechsler Intelligence Scale for Children (WISC-IV) for verbal and non-verbal intelligence; the Boston Naming Test, which evaluates a patient's ability to name images of objects with increasing difficulty; the Delis-Kaplan Executive Function System (D-KEFS); Letter Fluency and Category Fluency, for verbal fluency; DKEFS Trails, for visual motor-sequencing; and a Grooved Pegboard task to assess manipulation dexterity. Results for patients were compared with normative values for each of the tasks in order to determine if deficits were present.

Results from both fMRI and neuropsychological evaluations of POMS patients are compelling because they directly support the objectives of the study in demonstrating the usefulness of FMRI activation patterns for assessing POMS disease progression. For example, POMS1 demonstrates responses consistent with normal language functioning in all four of the language related tasks, and has expressive language localized to the normal region as revealed by fMRI. Similarly, POMS1 demonstrates a substantially impaired motor ability with their dominant hand, which meshes with the result from the motor fMRI that shows an abnormal, bilateral, non-localized motor activity. These observed congruencies between results obtained from fMRI and neuropsychological evaluation, as evidenced by participants: POMS1, POMS3, POMS4, POMS6 and POMS7 which show that both methods generally converge on a consistent evaluation of function. See Figure 3.

POMS	WISC-IV	Boston Naming	Letter Fluency	Category Fluency	DKEFS Trail	Pegboard D	Pegboard ND
1	90	93	10	12	9	74	91
2	105	93	7	10	12	104	95
3	73	70			13		
4	55	81				40	40
6	79	67	5	7	10	86	78
7	128	111	17	18		96	79
NORM (SD)	100 (15)	100 (15)	10(3)	10(3)	10(3)	100 (15)	100 (15)

Figure 3: 6 POMS patients' (labeled: POMS1, POMS2, POMS3, POMS4, POMS6, and POMS7) scores on normalized neuropsychological evaluations. Each patient was evaluated at a variety of tasks that demanded a level of either language (blue) or motor (orange) functionality. Scores that range below one standard deviation are considered borderline deficient, and are marked in pink, and scores that range two standard deviations below the mean are considered impaired, and are marked in red. Conversely, scores that range one standard deviation or more above the mean or more are marked in green. Some patients were unable to adequately engage in some of the tasks, and these are marked with grey cells. Normative values and standard deviations are included in the final row.

Notice in these findings that POMS2 has at least one result from one of the modalities that is at odds with the other. While the majority of cases show significant cross-modal consistency, case POMS2 illustrated an interesting result by demonstrating a normal language response in their neuropsychological profile, but at the same time the fMRI activity associated with these language tasks as assessed via fMRI is significantly abnormal. This may indicate a functional reorganization that has preserved function in the face of increasing MS lesion burden in this particular patient. As such, we have shown that fMRI is able to detect an abnormality associated with multiple sclerosis disease progression that is not yet clinically evident. These preliminary findings although carried out in a smaller cohort, support the hypothesis put forth under this project.

b) Subtask 3b. Nothing to report due to incomplete dataset.

iii. Task 4. In the second year of the funding period, we have acquired compelling preliminary data which have allowed us to submit 2 major research proposals for additional funding by way of investigator-initiated R01 proposals to The National Institutes of Health (NIH), including also a pending proposal to the Howard-Hughes Medical Foundation Faculty Scholar's Competition.

a) Subtask 4a. The following grant proposals were submitted in this funding period

1. "*Passive Functional Mapping for Pediatric Epilepsy Presurgical Planning*" 1R01NS092885-01A1, proposed start date: 4/1/2016, pending
2. "*Evaluating Neuropathogenic Mechanisms Leading to Disability in Multiple Sclerosis*" 1 R01 NS096211-01, proposed start date: 4/1/2016, pending

3. "*2016 Faculty Scholars Program Competition*", proposed start data: 11/1/2016, pending

c. **What opportunities for training and professional development has the project provided?**

i. The project has provided opportunities for training and professional development of a research assistant, Jack Hussey. This research assistant was trained to acquire and interpret fMRI data from healthy controls and patients with either multiple sclerosis or pediatric epilepsy. Additionally, he was invited to present at The Annual CRL Meeting, Harvard Medical School to discuss our fMRI in pediatric patients.

d. **How were the results disseminated to communities of interest?**

i. We are presently preparing two manuscripts for submission to peer-reviewed medical journals.

e. **What do you plan to do during the next reporting period to accomplish the goals?**

i. The main objective of our project in the next reporting period is to collect fMRI data on 5 remaining POMS patients, and 10 additional healthy controls in order to meet the targeted, 30 POMS patient and 40 controls. Once our study cohort is complete, we will at that point be in a position to perform the proposed group-level analysis comparing our novel measures of functional reorganization against patient performance in neuropsychological examinations, as such to complete and draw main conclusions from the study.

4. **IMPACT:**

a. **What was the impact on the development of the principal discipline(s) of the project?**

i. The preliminary findings from this study, Figures 1-3 above, have been presented in invited talks at Harvard Medical School.

b. **What was the impact on other disciplines?**

i. Over the 2015 funding period we have made significant impact using the fMRI methods we have developed in POMS patients under this project for the application also in presurgical epilepsy patients at our institution. We have explored fMRI for improving epilepsy surgical planning in pediatric patients. To that end we acquired and analyzed presurgical fMRI in 42 pediatric patients for the purposes of motor-specific and language-specific functional mapping. These clinical fMRI mappings provided the surgical team at our institution a view of their patient's brain functions in terms of left or right dominance, and in the location of function relative to the planned surgical site. This information offered surgeons the potential to

spare patients post-operative impairment in brain functions located near a planned surgical site. In many cases, our fMRIs helped to significantly improve post-surgical outcomes, or served as safer alternative to the invasive functional mapping techniques during the evaluation phase of those patients at our institution (Boston Children's Hospital).These research activities have had an enormous impact at our institution and have initiated the development of a new program which will be directed by Dr Ralph O. Suarez, the PI under this project.

c. **What was the impact on technology transfer?**

i. As we have developed fMRI techniques for successful fMRI mappings in pediatric POMS patients, these technologies have become useful also in transfer to pediatric epilepsy patients as well as tumor and intravenous malformation patients who were placed under consideration to undergo pediatric brain surgery at our institution.

d. **What was the impact on society beyond science and technology?**

i. We have noted that many of the readers and attendees to our dissemination activities—journal articles, abstracts, and presentations—have friends or family who suffer from pediatric brain disorders; these members of society have expressed their appreciation, awareness, and support of our research efforts aimed at improving the health of patients. This has impacted society positively.

5. **CHANGES/PROBLEMS:**

a. **Changes in approach and reasons for change**

i. Noting to report.

b. **Actual or anticipated problems or delays and actions or plans to resolve them**

i. Recruitment and fMRI scanning of POMS patients has been delayed by scheduling issues at the MRI scanners at our institution, and slower than expected recruitment of eligible POMS patients from the MS clinic. Recruitment and fMRI scanning of healthy control populations needs to wait until the POMS patient group is completed with respect to both fMRI and neuropsychological measures---as the control cohort must be age-, and sex-matched to the POMS cohort. We have resolved this issue by submitting a recently approved 12-month no cost extension to allow us the extra time needed to complete the study objectives.

c. **Changes that had a significant impact on expenditures**

i. Nothing to report

d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

i. Nothing to report

e. **Significant changes in use or care of human subjects**

i. Nothing to report

f. **Significant changes in use or care of vertebrate animals.**

i. Not applicable

g. **Significant changes in use of biohazards and/or select agents**

i. Not applicable

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

a. **Publications, conference papers, and presentations**
Report only the major publication(s) resulting from the work under this award.

i. **Journal publications:** Ralph O. Suarez, Vahid Taimouri, Katrina Boyer, Clemente Vega, Alexander Rotenberg, Joseph R. Madsen, Tobias Loddenkemper, Frank Duffy, Sanjay P. Prabhu, and Simon K. Warfield. "**Passive fMRI mapping of language function for pediatric epilepsy surgical planning: validation using Wada, ECS, and FMAER.**" *Epilepsy Res. 2014 Dec; 108(10):1874-88*. A*cknowledgement of federal support (YES)*

ii. **Other publications, conference papers, and presentations:**

a) Invited talk to The CRL Annual Meeting 2015. Talk titled "**Functional magnetic resonance imaging of pediatrics**" was presented by PI, Ralph O. Suarez on November 21, 2015. A*cknowledgement of federal support (YES)*

b) Invited talk to The CRL Annual Meeting 2015. Talk titled "**Functional magnetic resonance imaging in pediatric applications using motion-robust fMRI**" was presented by project RA, Jack Hussey on November 21, 2015. A*cknowledgement of federal support (YES)*

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

a. **What individuals have worked on the project?**

Name:	Ralph Suarez
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	9.6
Contribution to Project:	Dr. Suarez has carried the overall intellectual responsibility for the project.
Funding Support:	No change

Name:	Ferne Pinard
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.84
Contribution to Project:	Dr. Pinard has analyzed the neuropsychological test results and managed the database of these results.
Funding Support:	No change
Name:	Mark Gorman
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.84
Contribution to Project:	Dr. Gorman has been responsible for the recruitment of patients, and for the interpretation of data in a clinical context.
Funding Support:	No change

Name:	Sanjay Prabhu
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	0.24
Contribution to Project:	Dr. Prabu has reviewed the MRI of each subject and evaluated the appearance of white matter, cortical gray matter, and the number and location of lesions
Funding Support:	No change

Name:	Simon Warfield
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6
Contribution to Project:	Dr. Warfield has performed structural analysis of MRI data by the implementation of custom software and novel techniques
Funding Support:	No change

Name:	John Hussey
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Mr. Hussey has assisted in the recruitment of patients, collection of data, presentation of findings and other related tasks.
Funding Support:	none

b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

i. Noting to report

c. **What other organizations were involved as partners?**

i. Nothing to report

8. **SPECIAL REPORTING REQUIREMENTS**

a. **COLLABORATIVE AWARDS:** Not applicable

b. **QUAD CHARTS:** Not applicable

9. **APPENDICES:** Nothing to report.